A Phase 2, Randomized, Open-Label Study Comparing Oral Ixazomib/Dexamethasone and Oral Pomalidomide/Dexamethasone in Relapsed and/or Refractory Multiple Myeloma

Published: 14-09-2017
Last updated: 04-01-2025

Primary objective:To compare the effect of ixa+dex versus pom+dex on progression-free survival (PFS) in patients with relapsed and/or refractory multiple myeloma (RRMM) who have received at least 2 prior lines of therapy, including lenalidomide and...

Ethical review	Approved WMO
Status	Completed
Health condition type	Plasma cell neoplasms
Study type	Interventional

Summary

ID

NL-OMON48607

Source
ToetsingOnline

Brief title
C16029

Condition

- Plasma cell neoplasms

Synonym
Kahler's disease, Multiple Myeloma (MM)

Research involving

Human

Sponsors and support

Primary sponsor: Millenium Pharmaceuticals
Source(s) of monetary or material Support: sponsor/farmaceut

Intervention

Keyword: Ixazomib, Open-Label, Relapsed and/or Refractory Multiple Myeloma

Outcome measures

Primary outcome

Progression-free survival (PFS), defined as the time from randomization to the first occurrence of confirmed progressive disease (PD), as evaluated by the investigator, according to International Myeloma Working Group (IMWG) criteria, or death from any cause, whichever occurs first.

Secondary outcome

The secondary endpoints are OS, measured as the time from randomization to death from any cause; ORR (defined as complete response, very good partial response (VGPR), or PR [per IMWG criteria]); duration of response; time to response; time to progression (TTP); health-related QOL as measured by the physical domain of the EORTC QLQ-C30; health-related QOL as measured by other domains of the EORTC QLQ-C30, by the EORTC QLQ-MY20, and by the EQ-5D-5L; health care utilization as measured by the number and duration of medical encounters; and safety/tolerability.

After the primary endpoint of PFS has been met, all central efficacy and investigator assessments of response for protocol purposes will be discontinued; patients will be followed for survival and the appropriate data

collected.

Study description

Background summary

MM is a clonal disease of plasma cells that is characterized by the accumulation of plasma cells in the bone marrow (and other organs) and sometimes results in bone marrow failure, bone destruction, hypercalcemia, anemia, infection, and renal failure. It is the second most common hematological malignancy, constituting approximately 1% of all reported neoplasms and approximately 13% of hematologic cancers worldwide [9]. The incidence of MM is expected to increase over the next decade, which highlights the need for more effective MM therapies. Moreover, to a greater extent in the future than now, MM will be a disease that primarily affects older persons (those aged 64 to 84 years), who generally have a worse prognosis

MM remains an incurable disease for most patients and development of RRMM is an inevitable reality for almost all patients. While there is no widely accepted standard of care for RRMM, patients typically receive several lines of therapy with combinations of drugs over the course of their disease.

Ixazomib in combination with LenDex has been approved by the US FDA and other agencies for the treatment of patients with MM who have received at least 1 prior therapy [3,4]. The exploration of ixazomib for other therapeutic areas is ongoing. To date, activity in MM has been seen with single-agent ixazomib and with ixazomib combined with established therapies. In addition, single-agent activity has been observed in relapsed amyloidosis and indolent non-Hodgkin lymphoma.

Overall, ixazomib shows signs of antitumor activity, as evidenced by at least 50% reduction in disease burden in some patients, including patients that have been heavily pretreated as well as those with newly diagnosed MM, and prolongs stabilization of the underlying disease in other patients across all ongoing studies. Though additional data continue to be obtained to further establish the clinical benefit of this drug, the emerging data support the continued development of ixazomib for the treatment of patients with hematologic and solid tumor malignancies as well as ixazomib as part of doublet therapy for RRMM

Study objective

Primary objective:
To compare the effect of ixa+dex versus pom+dex on progression-free survival

(PFS) in patients with relapsed and/or refractory multiple myeloma (RRMM) who have received at least 2 prior lines of therapy, including lenalidomide and a proteasome inhibitor, and are refractory to lenalidomide but not refractory to proteasome inhibitors.

Secondary objectives:
• To compare overall survival (OS) in patients treated with ixa+dex versus pom+dex.
• To compare duration of response, overall response rate (ORR), time to response, and time to progression with ixa+dex versus pom+dex.
• To obtain health-related QOL data related to physical functioning of patients treated with ixa+dex versus pom+dex.
• To assess health-related QOL by additional function and symptom domains of the EORTC QLQ-C30 instrument and by the EORTC QLQ-MY20 and 5-level classification system of the EuroQol 5-Dimensional Health Questionnaire (EQ-5D-5L) instruments.
• To evaluate health care utilization by patients receiving ixa+dex versus those receiving pom+dex.
• To collect plasma concentration-time data for ixazomib to contribute to population pharmacokinetic characterization of ixazomib and to conduct exposure-response analyses for patients receiving ixa+dex.
• To compare safety/tolerability of ixa+dex to that of pom+dex.

Study design

Study C16029 is a randomized, open-label, phase 2 study. The 3 stratification factors are International Staging System stage (I or II vs III at study entry), prior lines of therapy (2 vs 3 or more), and age (<65 vs >=65 years). Patients will be randomized in a 3:2 ratio to receive ixazomib+dexamethasone (ixa+dex; Arm A) or pomalidomide+dexamethasone (pom+dex; Arm B), until first confirmed progressive disease (PD) or unacceptable toxicities.

Intervention

Arm A
Ixazomib will be administered at a 4 mg starting dose, with escalation to 5.5 mg at Cycle 2 for patients who tolerate the 4 mg dose in Cycle 1 (specifically, patients who do not experience any new Grade 1 peripheral neuropathy with pain or other ixazomib-related >=Grade 2 nonhematologic or >=Grade 3 neutropenia or thrombocytopenia in Cycle 1). Patients who have had any dose reductions, holds, or delays because of ixazomib toxicities will not dose escalate. Dose escalation beyond the start of Cycle 2 is permitted only when dose escalation was inadvertently missed at Cycle 2.
Ixazomib will be administered orally on Days 1, 8, and 15 of each 28-day cycle, combined with dexamethasone 20 mg (or 10 mg if patient is aged >=75 years) orally on Days 1, 2, 8, 9, 15, 16, 22, and 23 of each 28-day cycle until PD. In

cases where only 4 mg tablets for dexamethasone are available (eg, 4 mg dexamethasone is the only dosage available), the following dexamethasone schedule is recommended for patients aged >=75 years: 12 mg dexamethasone will be given on Days 1, 8, 15, and 22 of every 28-day cycle; and 8 mg dexamethasone will be given on Days 2, 9, 16, and 23 of every 28-day cycle.

Arm B
Pomalidomide will be administered at 4 mg orally on Days 1 to 21 of each 28-day cycle, combined with dexamethasone 40 mg (or 20 mg if patient is aged >=75 years) orally on Days 1, 8, 15, and 22 of each 28-day cycle until PD.

Study burden and risks

The more commonly occurring discomforts and risks are listed below:
• Low platelet count which may increase the chance of bleeding
• Skin rash which may range from some red areas, small flat spots, or small raised bumps that may or may not be itchy in a few areas or all over the body
• Feeling tired or weak
• Nausea
• Vomiting
• Diarrhea
• Numbness or tingling or pain feelings in hands and feet
• Constipation
• Lowered red cells or anemia which may make you feel tired;
• Lowered white blood cells called neutrophils that may increase your risk of infection and may be associated with fever

STUDY PROCEDURAL RISKS
In addition to the risks of all study medications, routine needle sticks for blood samples may cause pain, bruising and rarely, infection at the site where blood is drawn.
Possible side effects of bone marrow aspirate/biopsy include bleeding, infection, bruising, discomfort and/or pain at the aspirate site and possible side effects from the local anesthetic (pain or bruising at the injection site).
The X-ray, skeletal x-ray, MRI or CT scans associated with this study are typically the same number of times as if you were not in a clinical trial.
There are some side-effects or risks associated with these scans. Often subjects who have an MRI or CT scan experience feelings of claustrophobia (fear of being confined in any space). Also, the risk of radiation exposure from these scans is uncertain and has not been definitively determined.

Refer for an overview of the other Ixazomib side effects to section 8.8.1 of the Protocol
Refer for an overview of the Pomalidomide side effects to section 8.8.2 of the Protocol

Benefit:
It can increase the amount of time the patients live without worsening of the patients disease

Contacts

Public
Millenium Pharmaceuticals

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• Adult patients (aged >=18 years) who have been diagnosed with multiple myeloma (MM) according to standard criteria.
• All patients must have had a relapse or PD after having received 2 or more prior lines of systemic therapy. (A line of therapy is defined as 1 or more cycles of a planned treatment program; this may consist of 1 or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. For example, a planned treatment

approach of induction therapy followed by autologous stem-cell transplantation, followed by maintenance is considered 1 line of therapy. Typically each line of therapy is separated by PD.)
• All patients must be refractory to lenalidomide, defined as having received at least 2 consecutive cycles of lenalidomide as a single agent or within a lenalidomide-containing regimen and having had PD during treatment with or within 60 days after the last dose of lenalidomide. The starting dose of lenalidomide should have been 25 mg (or as low as 10 mg in the case of renal function impairment or other safety concern), and the final dose should have been a minimum of 10 mg.
• All patients must have received at least 2 consecutive cycles of a bortezomib- or carfilzomib-containing regimen, and either:
- Achieved at least a partial response (PR) and did not have PD during treatment with or within 60 days after the last dose of bortezomib or carfilzomib,
OR
- Had bortezomib and/or carfilzomib intolerance (defined as discontinuation because of drug-related adverse events (AEs) before completion of the planned treatment course) without PD upon the start of the next regimen.
• All patients must have an Eastern Cooperative Oncology Group score of 0 to 2.
• All patients must have measurable disease defined by serum M-protein >= 1 g/dL (>=10 g/L) or urine M-protein >=200 mg/24 hours and must have documented MM isotype by immunofixation (central laboratory).

Exclusion criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:
- Patients must not have received prior ixazomib or pomalidomide and must not have been a participant in a previous ixazomib clinical study.
- Prior allogenic bone marrow transplantation in any prior line of therapy or prior autologous SCT in the last prior line of therapy*unless the autologous SCT was
performed a year or more before disease progression.
- Female patients who are lactating and breastfeeding or have a positive serum pregnancy test during the Screening period.
- Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol,
such as life-threatening illness unrelated to cancer.
- Diagnosed with or treated for another malignancy within 2 years before randomization, or previously diagnosed with another malignancy and have any evidence of residual, persistent, or recurrent disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have

undergone complete resection.
- Diagnosis of smoldering MM (see Appendix D), Waldenström's macroglobulinemia, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome, plasma cell leukemia, primary amyloidosis, myelodysplastic syndrome, or myeloproliferative syndrome.
- Known allergy to any of the study medications or their analogues, or excipients in the various formulations.
- Peripheral neuropathy Grade 1 with pain or Grade 2 or higher peripheral neuropathy of any cause on clinical examination during the Screening period.
- Treatment with any investigational products or with chimeric or fully human monoclonal antibodies within 30 days before randomization, systemic anticancer therapy or radiotherapy within 14 days before randomization (Note: "spot" radiation for areas of pain is permitted), and major surgery within 14 days before
randomization.
- Known gastrointestinal disease or gastrointestinal procedure that could interfere with the oral absorption or tolerance of study therapy, including difficulty swallowing.
- Serious infection requiring parenteral antibiotic therapy or any other serious infection within 14 days before randomization.
- Central nervous system involvement with MM (by clinical symptoms and signs).
- Ongoing or active systemic infection, known human immunodeficiency virus-RNA positive, known hepatitis B surface antigen seropositive, or known hepatitis C virus-RNA positive.
Note: Patients who have positive hepatitis B core antibody can be enrolled but must have hepatitis B virus-DNA negative. Patients who have positive hepatitis C antibody can be enrolled but must have hepatitis C virus-RNA negative.
- Systemic treatment with strong cytochrome P-450 3A inducers (rifampin, rifapentine,rifabutin, carbamazepine, phenytoin, phenobarbital) or use of St. John's
wort within 14 days before randomization.
- Admission or evidence of illicit drug use, drug abuse, or alcohol abuse.
- History of severe cutaneous reactions, including hypersensitivity reactions such as Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN), and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), in the context of treatment with lenalidomide or thalidomide (see Section 8.7 of protocol for more information).

Study design

Design

Study phase: 2

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	22-02-2018
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ixazomib
Generic name:	Ixazomib
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	pomalidomide
Generic name:	Imnovid
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	14-09-2017
Application type:	First submission
Review commission:	METC Brabant (Tilburg)

Approved WMO

Date:	22-01-2018
Application type:	First submission
Review commission:	METC Brabant (Tilburg)

Approved WMO

Date:	26-04-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-05-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-08-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-09-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-03-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-03-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	16-04-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-08-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-08-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO	

Date:	28-11-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	16-12-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-09-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-09-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2016-004742-28-NL
CCMO	NL62127.028.17

Study results

Date completed:	01-06-2020

Results posted: 22-11-2022

First publication
18-07-2022